CLINICAL REVIEW MEMO

Subject: Ortec International, Inc. Composite Cultured Skin use in management of split thickness donor sites in burn patients (G990063 pivotal study), clinical comment summary: P010016 and P010016 A1, 2, 3.

Composite Cultured Skin (CCS) is a bi-layer skin substitute that consists of keratinocytes and fibroblasts derived by culture allograft of cells from the foreskin of neonates born to pre-screened and consenting mothers. The sponsor, Ortec International, Inc., has submitted P010016, which includes G990063 pivotal study report. P010016 review identified issues, which the sponsor has addressed in P010016 amendments 1, 2, and 3.

Herein please find brief clinical comments on P010016, as well as P010016 A1, 2, and 3.

G990063

Pilot Study

G990063 pilot study design was a single-center, matched pair / within-patient control, randomized study of the safety and preliminary effectiveness CCS compared to a commercially available device, Biobrane, in the management of split thickness donor sites in burn patients. Specifically, two anatomically matched split thickness donor site wounds per patient were assigned to be site 1 or site 2 per a standard protocol. A randomization code was determined for each split thickness donor site to designate treatment to the experimental (CCS) or control (Biobrane) device. Fifteen to twenty patients were to be enrolled; eight patients were enrolled. Based on analysis of data from five of seven pilot study patients who completed the 28-day follow-up assessment period, the observed median time to 100% re-epithelialization 21 days at the Biobrane treated split thickness donor sites, and 12 days at the CCS treated split thickness donor sites. Pivotal study designed was based on pilot study design and outcomes.

Pivotal Study

G990063 pivotal study was a matched pair / within patient control, multi-center study to demonstrate the superiority of CCS compared to control, Biobrane – L in

- The safety and efficacy of CCS to facilitate timely wound closure of split thickness skin donor sites in burn patients, compared to control, Biobrane - L.
- The functionality, durability of re-cropped skin serving as an autograft and time to complete (100% re-epithelialization) healing of the re-cropped and re-treated donor site in a subset of burn patients with massive surface area involvement who require re-harvesting as part of their complex wound and critical care management. (G990063s1, p15).

Inclusion Criteria

1. Age > /= 1 year
2. Birth control for women of child bearing potential
3. Total Body Surface Area (TBSA) burned = 10 = to 80%
4. Burns due to thermal, chemical or friction injury
5. Patients >/= 3 years of age
   - Minimum total donor surface area (TDSA) = 72 to 90 cm2 (one investigational device of 36-45cm2 and one control site of an equivalent area);
   - Maximum TDSA = 288 to 360 cm2 (4 investigational devices of 144 to 188 cm2 making up one test site and the control site of an equivalent area).

   Patients < 3 years of age:
   - Minimum TDSA = 36 to 45 cm2, assuming use of one-half of an investigational device (18 to 22.5 cm2) and one control site of equivalent area;
   - Maximum TDSA = 144 to 180 cm2, assuming use of two investigational devices measuring 72 to 90 cm2 as one test site and the control site measuring the equivalent area; each device measuring 36cm2 (6 cm x 6 cm) to 45 cm2 (6.7 cm x 6.7 cm).
6. Donor sites:
   - To be in not previously harvested skin and not healed superficial partial thickness burn wounds.
   - To be on non-articulated surfaces, including back, buttocks and scalp.
7. Split thickness donor sites to be
   - 0.006 to 0.014 inch in depth
   - Both donor sites to be same depth

- Treatment sites permitted to be slightly shallower: 0.004 – 0.014 inches if the sites were undergoing re-cropping.

8. Informed consent
9. Willingness to comply with protocol design
10. Life expectancy of at least six weeks after study entry.

Exclusion Criteria

1. Sepsis with hemodynamic instability requiring pressor support or a microbiology report of positive blood cultures drawn within48 hours prior to surgery.
2. Pregnant or lactating
3. Severe inhalation injury requiring PEEP > 20 and Fi02 > 60% within 12 hours prior to surgery.
4. Trauma Scores:
   Injury Severity Score (ISS)
   - ISS > 40 and age 15 to 49 years (y).
   - ISS > 29 and age 45 to 65 y
   - ISS > 25 and age > 65y

   If age < 15 y: Pediatric Trauma Score </= 5 or pediatric Glasgow Coma Scale score < 8
5. Treatment with systemic corticosteroids during the 30 days prior to injury.
6. Immunosuppressive, radiation or chemotherapy during the three months prior to injury.
7. Previous participation in a trial for management of donor sites.
8. Concurrent use of any investigational product on the burn sites.
9. History of allergy or sensitivity to collagen material
10. History of insulin-dependent diabetes accompanied by glycosylated hemoglobin A1C > 10%.

Donor Site Selection

Split thickness donor sites were to be selected according to the Principal Investigator's routine surgical practice, guided by donor site availability with attempt to identify to similar donor sites on each patient. Discrete, contiguous, no-articulated sites were used.

Treatments

- <u>Biobrane L</u>
  - Applied to the donor site, secured with staples, covered with gauze wraps.
  - Outer dressings generally removed after 24 – 48 hours post-operatively
  - Attempts to remove Biobrane L from newly formed epidermis generally began between post-operative day 7 and 10.
  - Areas where Biobrane L remained adherent after soaking were considered non-epithelialized and open.

- <u>CCS</u>
  - Applied to donor site, secured with staples as per investigator discretion, covered with non-adherent, moisture retentive synthetic material, gauze wrap and Ace conforming bandage.
  - Outer dressing removed after 72 hours post-operatively and then every 48 to 72 hours, and backing irrigated with saline until post-operative day 7 when backing removal was attempted.

Follow-up

- Screening, Day 0 (pre & post harvest), 3, 7, 14, 21, 28, week12, 24

Evaluation Parameters

- Safety
  - Adverse events
  - Scar outcome at 12 and 24 weeks by Vancouver Scar Scale: investigator evaluation
  - Scar outcome at 12 and 24 weeks by Hamilton Burn Scar Scale: photo-evaluation
  - Treated site pain, itching, infection
  - Donor site breakdown

- Effectiveness
  <u>Primary</u>
  Time to 100% wound healing by photography, evaluated in random order by three independent burn experts masked to study treatment.

Secondary

- Time to 100% wound healing by planimetry analyzed at a central laboratory masked to treatment assignment.
- Time to 100% wound healing by investigator evaluation
- Incidence of 100% wound healing
- Time to re-cropping

P010016 and P010016 A 2 & 3

Indication for Use: Ortec Inc., is seeking approval for CCS in the management of split thickness donor site wounds in burn patients. (P010016 A2, p1)

Sample size (prospective):
Seventy-five evaluable and 100 intent to treat patients; increased to 85 evaluable per amendment 3 (P010016V9, p 48).

Hypothesis:

- Null: Time to healing in both arms are the same (P010016 amendment 2, p204).
- Alternative: Time to healing in both arms of the study are not the same (P010016 amendment 2, p204).

Study Power:

- Prospective Power (EVL cohort, n = 84; 0.05 alpha): 80%(P010016 amendment 2, p202)

Expected Time to 100% epithelialization with CCS: 17.5 days (P010016 amendment 2, p202)
Expected Time to 100% epithelialization with Biobrane-L: 27 days (P010016 amendment 2, p202)
Difference in Expected Time to 100% epithelialization: Biobrane minus CCS = 9.5days

- Post-hoc Power (ITT cohort, n = 82; 0.05 2-sided alpha): 90% (P010016 amendment 2, p203)

Observed Time to 100% epithelialization with CCS: 18.0 days (P010016 amendment 3)
Observed Time to 100% epithelialization with Biobrane-L: 22.4 days (P010016 amendment 3)
Difference in Observed ITT cohort Time to 100% epithelialization: Biobrane minus CCS = 4.4 days

Post-hoc Power (PPT cohort, n = 72; 0.05 2-sided alpha): 85% (P010016 amendment 2, p203)
Observed Time to 100% epithelialization with CCS: 17.8 days (P010016 amendment 3)
Observed Time to 100% epithelialization with Biobrane-L: 22.1 days (P010016 amendment 3)
Difference in Observed PPP cohort Time to 100% epithelialization: Biobrane minus CCS = 4.3 days

Post-hoc Power (EVL cohort, n = 60; 0.05 2-sided alpha): 93% (P010016 amendment 3)
Observed Time to 100% epithelialization with CCS: 16.9 days (P010016 amendment 3)
Observed Time to 100% epithelialization with Biobrane-L: 22.3 days (P010016 amendment 3)
Difference in Observed EVL cohort Time to 100% epithelialization: Biobrane minus CCS = 5.4 days

The sponsor states that (P010016 amendment 2, p205) "at the time the decision was reached to stop the study due to decreased enrollment rate, approximately 90% of the patients achieved 100% healing. It was assumed that the remaining patients would continue to 100% healing and that the sample size of between 75 to 80 patients would be sufficient to achieve statistical significance." The trial was stopped early, in May, 2000.

It is unclear when study blind to the sponsor was broken and analysis undertaken.

Patient Accounting (Tables 11.1.1; C1, C2)
G990063 pivotal study was designed for 100 Intent to Treat (ITT) patients with expectation of 25% loss to follow so as to provide a 75 patient Evaluable (EVL) cohort. Table C1 states that the study enrolled an 82 patient ITT cohort and a 75 patient Evaluable (EVL) cohort. Table C2 demonstrates that 60 patients completed study, are evaluable. However, efficacy, is presented on the basis of a "per protocol" population, which has 74 patients. The Per Protocol population is defined as a subset of the Intent to Treat population which had no major protocol violations, and sufficient planimetry data to determine time to wound healing. This population is stated to have been defined by the sponsor, internally, on November 13, 2000, at which time the sponsor states that decision was also made to include seven steroid - treated patients in the study. Steroid treated patient were to have been excluded from study by study

inclusion / exclusion criteria. The Per Protocol Population is a retrospectively defined cohort: not addressed in the original protocol or subsequent communications with FDA.

Patient Accounting

N	
Prospective sample size: ITT	100
Prospective sample size: EVL	85
Enrolled: ITT	82
Completed study: EVL	60
Major Protocol Violations	8
Discontinued	22
• Adverse event	3
• Protocol violation	0
• Withdrew consent	0
• Lost to Follow-up	16
• Other	3
Efficacy, "Per Protocol"	74
Safety	82

*P010016v9, Tables 11.1.1; C1, C2

Demographics (P010016 v9 p52, 120 – 123, and P010016 A3)
Data is presented for gender, and race, as well as mean age, height and weight with standard deviation. Data is also presented for daily caloric requirements, Injury Severity Score, Pediatric Trauma Score, and Pediatric Glasgow Coma Score. Summary of donor site location, surface area, and autograft thickness were presented for all patients and per patient. Data represents pre-dominantly Caucasian male adults (age 15-65 years) with median height: 67 inches, weight: 160 pounds; median ISS: 11.0. Median Pediatric Trauma Score was 8.5; median Pediatric Glasgow Coma Score was 15.0. Most (74%) donor sites treated with CCS or Biobrane were located on the thigh. Appendix 1 to this review presents data.

Effectiveness

Primary

Time to 100% wound healing by photography, evaluated in random order by three independent burn experts masked to study treatment.

Secondary

- Time to 100% wound healing by planimetry analyzed at a central laboratory masked to treatment.
- Time to 100% wound healing by investigator evaluation
- Incidence of 100% wound healing
- Time to re-cropping

- Time to 100% wound healing, Days

Methods of assessment for the ITT (Intent to Treat) and PPP (Per Protocol Population censored at 32days) presented different mean and median time to 100%, however, with consistent trend:

	Clinical			Planimetry			Photography		
ITT	CCS	Biobrane	p	CCS	Biobrane	p	CCS	Biobrane	p
Median*	12.0	16.0	<0.0001	12.0	17.0	<0.0001	15.0	22.0	0.0006
Mean*	13.2	18.4	<0.0001	13.7	19.3	<0.0001	18.0	22.4	<0.0001
PPP									
Median*	12.0	16.0	<0.0001	12.0	16.0	<0.0001	15.0	21.0	0.0009
Mean*	12.9	17.9	<0.0001	13.4	18.7	<0.0001	17.8	22.1	<0.0001

*P010016, v9, p54-7.

Methods of assessment presented for the ITT population per investigator (P010016, A2) demonstrate differences amongst investigators and between methods that are greater than differences between treatment cohorts. Trends, however, demonstrate time to 100% wound healing to range from no difference between CCS and Biobrane, e.g.,

per investigators 4, 13 and 14 in median time to healing clinical assessment by investigator (P010016, A2, p3) to shorter time to 100% wound healing with CCS than Biobrane. No method or site / investigator mean or median assessment demonstrated shorter time to 100% wound healing with Biobrane than with CCS.

Median and mean with standard deviation for time to 100% from planimetry by investigator:*

		ITT	
	n	CCS	Biobrane
1	19	14.0; 14.2 (4.22)	26.0; 23.7 (7.59)
2	1	10.0; 10.0 (-)	14.0; 14.0 (-)
3	9	14.0; 15.3 (4.24)	28.0; 25.6 (6.88)
4	16	11.0; 11.3 (3.04)	11.5; 12.8 (4.75)
5	3	9.0; 16.0 (13.9)	11.0; 17.3 (12.7)
6		-	
7	7	12.0; 11.3 (2.14)	15.0; 18.4 (8.12)
8	9	11.0; 13.2 (7.24)	14.0; 18.2 (8.35)
9		-	-
10		-	-
11		-	-
12	2	- ; 23.5 (12.0)	- ; 23.5 (12.0)
13	3	20.0;19.7 (9.50)	20.0; 22.0 (6.24)
14	3	16.0; 15.7 (1.53)	16.0; 15.7 (1.53)
15	10	11.0; 12.9 (7.26)	16.0; 18.2 (9.67)

*P010016, v9, p147

Statistical assessment by the sponsor states that data is poolable across centers. Please refer to FDA statistical review for FDA statistical interpretation.

Time to 100% wound healing by photography, evaluated in random order by three independent burn experts masked to study treatment: correlation between masked assessors was requested well as per patient evaluation by each assessor. Per patient evaluation per masked photo reviewer was not provided. The sponsor has stated that two of the three agreeing photo analyses were used in determining the photographic endpoint. Kappa correlation coefficient for time to wound healing has been provided for amongst investigators and methods and indicates acceptable correlation. It is not stated, if kappa correlation was determined for all photo evaluations by all three assessors, or for the two of three in closest agreement.

	Kappa	95% LL	95% UL
Photographic Reviewers:			
PR1 / PR2	0.8313	0.8000	0.8627
PR1 / PR3	0.8564	0.8272	0.8855
PR2 / PR3	0.8974	0.8723	0.9225
Methods			
Photography / Planimetry	0.7324	0.6910	0.7739
Photography / Investigator	0.7269	0.6854	0.7684
Investigator / Planimetry	0.9563	0.9379	0.9748

The sponsor states that photography produced the greatest number of healing times beyond 32 days for both CCS and Biobrane because if photographs did not agree with the investigator assessment of 100% wound healing the next follow-up was not until two to six months, resulting in an artificially extended time (P010016, v9, p44).

Photo evaluators' report of incidence, mean, median and range of time to 100% wound healing (P010016 A3 and appendix 3 of this review) is higher for incidence of 100% wound healing and shorter for mean time to 100% wound healing for both CCS and Biobrane as performed by photo-evaluator 1 then by photo-evaluators 2 and 3. Final scores were determined by the best of 2 of 3 evaluations per patient. Median time to 100% wound healing, and relative difference between CCS and Biobrane are comparable amongst the three evaluators.

Time to 100% wound healing covariate analysis was requested and response provided (P010016 A2, p67-7) states that age, race and total body surface are burned are significant co-variates for the ITT population and variably for

censored and uncensored per protocol populations. Dexamethasone use, center, gender, trauma scores, and location of donor site are not identified as significant co-variates. Please refer to FDA statistical review for further interpretation of co-variate analysis. Time to 100% wound healing for various subgroups, for ITT and PPP cohort gender, age, and race, and by planimetry and photography for ITT cohort age, TBSA, and wound area, without analyses of interaction, was presented in e.g., tables: E1.5, E2.5, P9-A, B, C, and P11-A, B, C.

ITT (PPP)**	n	Median, days			Mean, days		
		CCS	Biobrane	Difference*	CCS	Biobrane	p
Gender							
Male	63	12.0 (12.0)	17.0 (16.0)	5.0 (4.0)	13.7	19.4	0.0002
Female	19	12.0 (12.0)	19.0 (16.0)	7.0 (4.0)	13.9	19.2	0.1083
Age							
<15 yo	22	12.0 (12.0)	14.0 (14.0)	2.0 (2.0)	12.2	15.3	0.1779
15 – 65 yo	57	13.0 (13.0)	20.5 (17.5)	6.5 (3.5)	14.0	20.6	<0.0001
>65 yo	3	16.0 (16.0)	29.0 (29.0)	13.0 (13.0)	19.0	25.7	0.6547
Race							
White	44	12.0 (12.0)	16.0 (15.0)	4.0 (3.0)	13.1	17.6	0.0195
Afro-American	20	14.0 (14.0)	23.0 (23.0)	9.0 (9.0)	15.0	22.4	0.0006
Other	18	12.0 (12.0)	16.0 (15.0)	4.0 (3.0)	13.9	20.1	0.1797
TBSA							
< 20%	21	12.0	14.0	2.0	11.8	13.6	0.3841
20 – 40%	47	12.0	21.0	9.0	14.1	20.5	< 0.0001
>40%	14	15.0	25.0	10.0	18.0	15.4	0.0290
Donor Area							
</= 45	20	12.0	15.0	3.0	11.9	17.3	0.0719
>45	62	13.0	18.0	5.0	14.3	20.0	0.0001

*Median days to 100% wound closure: CCS minus Biobrane **data in ( ) are for the PPP cohort.

Differences in between genders, age groups, and races are noted, however, inconclusive due to the small sample size of e.g. patients over age 65 (n=3) and potential co-variate effects such as total body surface area burned. From data provided, overall statistical significance appears to driven by outcomes for patients who are male, more than 15 years old, with TBSA 20 –40%, and with donor area greater than 45cm2. Per patient details are also provided in the four page summary chart in Appendix 2 of this review. Please refer to FDA statistical review for detailed interpretation of co-variate analysis presentation in P010016, A3.

- Incidence of 100% wound healing.

Incidence of 100% wound healing is presented in

- Kaplan Meier Estimates of Percentage Patients with 100% wound closure from Planimetry
  - CCS: 94.07% patients healed by day 29, censored analysis.
  - Biobrane: 82.45% patients healed by day 32, censored analysis.

- Donor sites with > 32 days to healing (P010016, v9, p44)

	CCS	Biobrane
Clinical	1	11
Planimetry	3	11
Photography	7	22

Incidence evaluated by photo evaluator 1 is higher than as determined by photo evaluators 2 and 3 who are comparable. The difference between CCS and Biobrane, however, is comparable amongst photo evaluators. (P016001 A3 and appendix 4 of this review).

- Time to re-cropping

Mean and median time to readiness for re-cropping is reported in P010016 (V9, p151). Time to readiness for re-cropping from day of device placement and day of 100% wound healing is reported in P010016 Table 13 and 14.

	n	CCS	Biobrane
ITT*			

Median	82	14.0	21.0
Mean	82	15.9	20.8
PPP**			
Median		14.0	20.4
Mean		15.6	20.0
***From day of device placement			
Median	82	15	21
Mean	82	18.01	43.05
***From day of 100% healing			
Median	82	1	1
Mean	82	3.82	17.14

*P010016, V9, p151
**P010016, V9, p152
***All patients: P010016, A3, Tables 13 and 14.
Of the 82 enrolled patients, 3 CCS sites (patient 01-009; 08-005; 03-001) and one Biobrane site (patient 01-009) are reported to have been re-cropped (P010016 A2, p156). Two of the CCS re-cropped sites received CCS and each is reported to have healed by day9; however, the graft recipient site for one patient (08-005) is stated to had not healed by day 14 and no further follow-up is reported; and the graft recipient site for the second patient is stated to have not been followed except for report that the donor and recipient sites were healed at 24 weeks and 6 months later. Patient 01-009 re-cropped sites were treated with Beta Glucan Collagen dressing s and the re-cropped donor site graft recipient site healing data was not captured. *The limited data precludes conclusions; post-market study is warranted to assure acceptable healing of recropped sites and take of grafts from re-cropped sites.*

Safety
Adverse Events at Donor Sites: number (%)*

	CCS	Biobrane
	N = 82	N = 82
Application site reaction	1 (1.2%)	1 (1.2%)
Pain	4 (4.9%)	4 (4.9%)
Infection	1 (1.2%)**	1 (1.2%)**
Surgical site reaction	1 (1.2%)	1 (1.2%)
Bullous eruption	0.00	1 (1.2%)
Pruritis	4 (4.9%)	5 (6.1%)
Pustular rash	1 (1.2%)	0.00

*P010016 A2, p164
**same patient:
CCS site: rare gram negative bacilli; rare gram-positive cocci in pairs; treated with Bactroban; resolved
Biobrane site: rare gram negative bacilli; treated with Bactroban; resolved.

The profile of adverse events at the donor sites includes events considered to be mild – moderate and is comparable for CCS and Biobrane. No severe or life threatening adverse events are reported at the donor sites. Systemic adverse events are listed (P010016 A2, p160-163 and appendix 3 to this review), however, device relation is precluded as all patients received both devices concurrently. Systemic effects of CCS use are confounded by the within patient control.

The adverse event of pustular rash is stated (P010016 A2, p158) to have occurred in a two year old male who received two 6 x 6 cm2 pieces of CCS to cover a donor site on his right thigh, and noted by parents on day 26 after CCS placement (October, 1999). The investigator is said to have attributed the rash to contact dermatitis from pressure garments being worn for scar management, and treated the rash with Eucerin and Bacitracin for one month, with rash resolution in without sequelae in two months (December, 1999).

The number of patients with signs of infection, breakdown / blistering, and itching are listed separately (P010016 v9, p69; as well as A3 Tables 4, 13 and 14). At this time, it is not clear how itching as a non-adverse event and

pruritis as an adverse event were distinguished. Scar evaluation by the investigator was performed at 12 and 24 weeks using the Vancouver Burn Scar Scale, and by three photo evaluators using the Hamilton Burn Scar Score (P010016 v9, p67 – 68 and summary tables; P010016 A3 Tables 2, as well as appendix 3 to this review).

Data source and IIT cohort outcomes are briefly summarized:

- Infection was recorded as present or absent, along with signs of infection which were evaluated as the presents or absence of purulence, warmth, malodor, erythema, tenderness to palpation, induration, swelling, and localized pain exceeding expected post-operative discomfort. If infection was present, whether or not culture was performed was recorded. Infection was reported in one patient. The number of patients with signs of infections is comparable and the difference is not associated with a difference in incidence of infection.

- Breakdown was recorded as percentage of breakdown at treatment site. Breakdown is reported at 4 CCS and 8 Biobrane sites. Breakdown per elapsed study day is presented from day six through thirty three and demonstrates a different time profile for breakdown at CCS and Biobrane sites: breakdown at CCS sites was noted at days 10, 11 and 13, while breakdown at Biobrane sites was noted at days 22, 28, and 33. Two incidences of breakdown at the CCS sites are noted to have occurred two days after 100% healing at the CCS treated site (P010016 A3 Table 13). Six incidences of breakdown at Biobrane sites were noted to have occurred at 4 to 20 days after 100% healing at the Biobrane treated site (P010016 A3 Table 14

- Itching was recorded as absent, mild, moderate, or severe. Breakdown by age and for censored as well as uncensored, ITT and PPP cohorts (P010016 A3 and appendix 3 of this review), as well as per patient. Profiles are presented (P010016 A3 and appendix 3 of this review).

- Pain was assessed with the Wong-Baker Faces pain rating scale for patients more than three years old and visual analog scale with numeric markings for intensity (0 to 10: 0, no pain; 5, moderate pain; 10, worse possible pain). Assessment is presented for various age groups and time periods

- Scar assessment by Vancouver Burn Scar Score (score range = 0 – 15) by investigators indicates clinically comparable scores for CCS and Biobrane treated sites at 12 weeks (CCS mean less than 1 point lower than Biobrane mean; medians equal: 2), and CCS treated sites' median (2 of 15) points lower than the Biobrane treated sites' median score (4 of 15). The clinical significance of the difference in median Vancouver Burn Scar Score at 24 weeks is not consistent with changes in the Hamilton Burn Scar Score. Hamilton Burn Scar Score assessment was performed by assessment of photographs taken at 12 and 24 weeks and randomly assessed by three independent photo evaluators. Photo-evaluator 1 assessed lower scores for CCS and Biobrane sites than photo evaluators 2 and 3 whose assessments were more clinically comparable. This trend was found for assessment of incidence and time to 100% wound healing. Overall Hamilton Burn Scar median scores were equal (Hamilton Burn Score = 2) for CCS and Biobrane treated sites at 24 weeks. As the unmasked (Vancouver / investigator) and masked (Hamilton / photo – evaluator) burn scar scores while not consistent in trend, both demonstrated approximate scores, scar outcome at CCS and Biobrane treated sites is clinically comparable.

	CCS	Biobrane	p
Sign of Infection			
Absent	81 (98.9%)	79 (96.3%)	0.157
Present	1 (1.2%)	3 (3.7%)	
N evaluated	82 (100%)	82 (100%)	
Signs of breakdown / blister			
Absent	76 (95.0%)	71 (89.9%)	0.248
Present	4 (5.0%)	8 (10.1%)	
N evaluated	80 (100%)	79 (100%)	
Itching			
None	22 (27.8%)	25 (31.3%)	0.414
Mild	29 (36.7%)	28 (35.0%)	
Moderate	21 (26.6%)	21 (26.3%)	
Severe	7 (8.9%)	6 (7.5%)	
Total	79 (100%)	80 (100%)	
Mean Pain, age > 8			
Mean (of means)	1.4	1.8	

Standard Deviation	1.7	1.8	
Range	0 – 9.0	0 – 9.0	
Median (of means)	1	1.2	
N, evaluated	56	57	
Vancouver Scar*			
Week 12, n	54	54	
Mean	2.26	3.07	0.017
Median	2	2	
Week 24, n	55	56	
Mean	2.56	3.79	0.002
Median	2	4	
Hamilton Scar Score**			
Week 12, n	55	55	
Mean	3.89	4.95	0.018
Median	3	5	
Week 24, n	48	50	
Mean	2.46	3.5	0.020
Median	2	2	

by investigator
**by three photo evaluators

Conclusion
Ortec Inc. has presented outcomes of a matched pair / within patient control, multi-center study to demonstrate the superiority of CCS compared to control, Biobrane – L in the safety and efficacy of CCS to facilitate timely wound closure of split thickness skin donor sites in burn patients, compared to control, Biobrane - L.

This study was also to assess the functionality, durability of re-cropped skin serving as an autograft and time to complete (100% re-epithelialization) healing of the re-cropped and re-treated donor site in a subset of burn patients with massive surface area involvement who require re-harvesting as part of their complex wound and critical care management. However, of the 82 enrolled patients, only three patients had 3 CCS sites (patient 01-009; 08-005; 03-001) re-cropped and only one patient had a Biobrane site (patient 01-009) re-cropped. Of the three re-cropped CCS sites only two re-cropped sites received CCS.